

REMARKS/ARGUMENTS

With this amendment, claims 1-5 and 11-15 are pending. For convenience, the Examiner's rejections are addressed in the order presented in a March 8, 2005, Office Action.

I. Status of the claims

Claim 1 is amended to recite a method of screening for a bioactive agent that modulates USP-25 protein peptidase activity on a USP-25 target protein which is conjugated to ubiquitin. Certain typographical errors have also been corrected. Support for these amendments is found throughout the specification, for example, at page 10, lines 4-5 and 11-12 and at page 45, line 22. Claim 2 is amended to include UBC9 protein. Support for this amendment is found throughout the specification, for example, at page 10, lines 8-9 and 15-16. Claim 3 is amended to be an independent claim, incorporating the aspects of prior claims 1 and 2, but specifying the ubiquitin-like proteins. Claim recites ubiquitin-like protein specific peptidase. Support for this amendment is found throughout the specification, for example, at page 45, line 22. Claim 11 is amended to depend from claim 1. Claim 13 is amended to depend from claims 2 or 12. Claim 14 is amended to depend from claim 1 or claim 11 and to correct a typographical error. These amendments add no new matter.

II. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 1-5 and 11-15 are rejected under 35 U.S.C. §112, first paragraph for allegedly lacking enablement. According to the Office Action, the specification does not enable one of skill to make and/or use the invention commensurate in scope with the claims. The Office Action also alleges that undue experimentation is required to practice the claimed invention. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The Office Action alleges that the specification does not enable use of a genus of target proteins fused to ubiquitin or to ubiquitin-like protein, and that therefore, undue experimentation would be required to practice the claimed invention. As set forth in the Manual

of Patent Examining Procedure (MPEP) § 2164.01, "the test of enablement is not whether any experimentation is necessary, but whether... it is undue." Further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. *See, e.g., In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971).

Claim 1 is now amended to recite identification of modulators of USP-25 protein ubiquitin-specific peptidase activity by, *e.g.*, determining the level of ubiquitin-conjugated target protein in the presence and absence of said candidate bioactive agent. Those of skill would recognize that ubiquitin-conjugated target proteins include polymers of ubiquitin. For example, polyubiquitin has been used as a substrate in assays of USP protein activity for many years and those assays were well-known to those of skill in the art at the time of filing. In addition, Claim 3 is amended to be independent and to recite ubiquitin-like protein specific peptidase activity, specific target proteins, and conjugation to specific ubiquitin-like proteins. These assays are enabled in the specification both because they are well known and, as described below, because of the citation of references that describe the assays in detail. According to the Federal Circuit Court of Appeals, "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01 *citing In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984). Thus, the disclosure meets the standards of enablement under US patent law.

The Office Action's concern regarding the use of alleged "variant" target proteins is misplaced. All that is needed to assay USP-25 peptidase activity is a ubiquitin protein conjugated to a second protein, including, *e.g.*, another ubiquitin or a chain of such molecules. Thus, the defining characteristic of a target protein is the presence of a ubiquitin protein. Target proteins also encompasses the well known conjugates of ubiquitin and ubiquitin-like proteins, *e.g.*, polyubiquitin. Because ubiquitin and assays of ubiquitin-specific peptidase activity toward

those proteins were very well known at the time of filing, any experimentation required to practice the claimed methods is not undue. Similarly, undue experimentation is not required to perform the methods of claim 3 directed to specific target proteins conjugated to specific ubiquitin-like proteins.

For example, polyubiquitin proteins have been known for almost 20 years. *See, e.g., Ozkaynak et al., EMBO J. 6:1429-1439 (1987).* Ozkaynak *et al.* discloses the nucleic acid and amino acid sequences of UBI4, a chain of 4 ubiquitin proteins. The disclosure of these sequences is sufficient to allow one of skill to make the protein. Ozkaynak *et al.* is cited in the specification at page 4, lines 9-10. UBP1, the first member of the family of ubiquitin specific proteases, *i.e.*, the family of proteins that includes USP-25, was discovered almost 15 years ago. *See, e.g., Tobias and Varshavsky, J. Biol. Chem. 266:12021-12028 (1991).* Tobias and Varshavsky disclose assays for ubiquitin peptidase (or protease) using UBP1 and UBI4 at Figure 4D, page 12026. Tobias and Varshavsky is cited in the specification at page 4, lines 19-20. Polyubiquitin conjugated to generic target proteins can also be used to assay for ubiquitin peptidase activity. *See, e.g., Baek et al., J. Biol. Chem. 272:25560-25565 (1997).* Assays of specific target proteins conjugated to polyubiquitin, *e.g.*, UBC9, SYK and calcineurin, can be performed in a similar manner. Baek *et al.* disclose ubiquitin peptidase (isopeptidase) activity using polyubiquitinated lysozyme as a substrate at Figure 7, page 25564. Baek *et al.* is cited in the specification at page 4, line 21. Di- and tri-ubiquitin have also been used as substrates of UBP proteins. *See, e.g., Figure 3 of Lin et al., Mol. Cell. Biol. 20:6568-6578 (2000).* Lin *et al.* is cited in the specification at page 49, lines 28-29.

The specification also enables generation of ubiquitin conjugated proteins at page 48, lines 23-30 and page 50, lines 1-3. The specification also notes that ubiquitin peptidase is used interchangeably with ubiquitin isopeptidase and ubiquitin-specific protease at page 14, lines 35-36 and at page 15, lines 13-15. This passage on page 15 also indicates that these enzymes remove ubiquitin from a substrate.

Based on the disclosures of Ozkaynak *et al.*, Tobias and Varshavsky, Baek *et al.*, and Lin *et al.* assays of USP-25 activity using *e.g.*, a polyubiquitin substrate were known to those

of skill at the time of filing. Each of the four references is cited in the application and each is provided for the Examiner in Exhibits A, B, C, and D. The specification expressly incorporates all cited references in their entirety at page 67, lines 9-10. Therefore, based on the knowledge of those in the art at the time of filing and the disclosure of the specification, the claimed methods are enabled.

In view of the above amendments and arguments, withdrawal of the rejection for alleged lack of enablement is respectfully requested.

III. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 1-5 and 11-15 are rejected under 35 U.S.C. §112, first paragraph, because the claimed subject matter is allegedly not described in the specification in a manner to convey to those of skill that the inventors had possession of the invention at the time of filing. According to the Office Action, the claims recite a genus of target proteins that is allegedly not described. Also according to the Office Action, there is allegedly no correlation between a USP-25 target protein and the recited USP-25 activity. To the extent the rejection applies to the amended claims, Applicants respectfully traverse.

According to the MPEP, possession can be demonstrated in a variety of ways. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. MPEP 2163, citing, *Pfaff v. Wells Elecs., Inc.*, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); and *Amgen, Inc. v. Chugai Pharmaceutical*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). Furthermore, the description need only describe in detail that which is new or not conventional. See *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986); M.P.E.P. 2163

The requirement for description of nucleic and amino acids can also be met in a variety of ways. The Federal Circuit Court of Appeals recently held that nucleotide sequences of known DNA sequences of known function do not need to be repeated in a patent application to meet the written description requirement. That is, for nucleotide sequences known in the art, a reiteration of the sequence in a patent specification is not required to meet the written description requirement. *Capon v. Eshhar*, No. 3-1480, slip op. at 15 (Fed. Cir. August 12, 2005). By analogy, the amino acid sequences of known proteins are also not required to meet the written description requirement.

As described above, all that is needed to assay USP-25 ubiquitin-specific peptidase activity is a ubiquitin protein conjugated to a second protein, including, *e.g.*, another ubiquitin or a chain of such molecules. Thus, the defining characteristic of a target protein is the presence of a ubiquitin protein. Target proteins also encompasses the well known conjugates of ubiquitin, *e.g.*, polyubiquitin. Assays of ubiquitin specific peptidase activity were well known in the art, as were the sequence of ubiquitin and therefore polyubiquitin and Exhibits A, B, C, and D are presented as evidence of this. Based on these references, those of skill would know what is meant by ubiquitin and polyubiquitin without additional disclosure in the specification. Therefore, those of skill would understand that the inventors were in possession of the invention at the time of filing.

The Office Action also alleges that there is no correlation between a USP-25 target protein and the recited USP-25 activity. The claims are amended to recite assay of USP-25 protein ubiquitin-specific peptidase activity or ubiquitin-like protein specific peptidase activity, which encompasses activity on either ubiquitin-conjugated or ubiquitin-like protein-conjugated target proteins, as supported in the specification, for example, at page 10, lines 4-5 and 11-12 and at page 45, line 22. Therefore, the claimed USP-25 protein ubiquitin-specific peptidase activity or ubiquitin-like protein specific peptidase activity correlates with the recited ubiquitin-conjugated or ubiquitin-like protein-conjugated target proteins.

In view of the above amendments and arguments, withdrawal of the rejection for alleged lack of written description is respectfully requested.

IV. Rejections under 35 U.S.C. §112, second paragraph

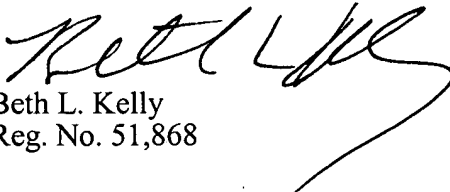
Claims 1-5 and 11-15 are rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to distinctly point out and claim the subject matter regarded by the applicant as the invention. According to the Office Action, the term "protein activity" is vague and indefinite. In order to expedite prosecution, claim 1 is amended to recite USP-25 protein ubiquitin-specific peptidase activity. Claim 3 is now amended to recite ubiquitin-like protein specific peptidase activity. In view of this amendment, withdrawal of the rejection for alleged indefiniteness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,


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